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Case Report

Long Survival after Resection of Small Cell Carcinoma of the Pancreas with Synchronous Adenocarcinoma of the Ampulla of Vater

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Abstract

Introduction: Small cell carcinoma of the pancreas is very rare and the patient usually died within one year after diagnosis.

Presentation of Case: We reported an unusual case of small cell neuroendocrine carcinoma of the pancreas and a synchronous moderately differentiated adenocarcinoma of the ampulla of Vater in a 44-year-old male, who was successfully treated with pylorus-preserving pancreaticoduodenectomy and post-operative cisplatin-based chemoradiation therapy.

Conclusions: The follow-up data showed no evidence of recurrence and the patient is in a good health condition at 117 months after the surgery.

Keywords:Small Cell Carcinoma; Pancreas; Adenocarcinoma; Ampulla of Vater

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Introduction

Pancreatic neuroendocrine neoplasms are uncommon and represent 1% to 2% of all pancreatic neoplasms [1, 2]. In the 2010 World Health Organization (WHO) Classification, pancreatic neuroendocrine neoplasms are classified into well-differentiated [low to intermediate grade) neuroendocrine tumor (NET) and poorly differentiated (high grade) neuroendocrine carcinoma (NEC) based on the number of mitoses and/or Ki-67 labeling index [1]. Based on this classification, low-grade (Grade 1) pancreatic NETs have <2 mitoses per 10 high power fields (HPF) and/or ≤2% Ki-67 index; intermediate grade (Grade 2) pancreatic NETs have 2 to 20 mitoses per 10HPF and/or 3% to 20% Ki-67 labeling index; and high-grade pancreatic NECs have >20 mitoses per 10HPF and/or >20% Ki-67 labeling index [3]. High-grade pancreatic NECs are further classified into small cell NEC and large cell NEC based on the cytologic features [1]. Both small cell NEC and large cell NEC of the pancreas are rare malignant pancreatic neuroendocrine neoplasms and are highly aggressive. Due to the rarity of high-grade pancreatic NECs, little is known about their biology and clinical outcome. Previous studies of high-grade pancreatic NECs are mostly case reports and small series [1-5]. Patients with high-grade pancreatic NEC usually presents at the advance stage, which is not resectable at the time of diagnosis and virtually all patients died within one year of the diagnosis [1-4]. Here, we present an unusual case of small cell NEC in the head of the pancreas with a synchronous adenocarcinoma of ampulla of Vater, who had a long survival (117 months) after successful pancreaticoduodenectomy and adjuvant chemoradiation therapy.

Case Presentation

A 44-year-old male presented with painless jaundice and a 30 pound weight loss over a two-month period. Computed tomographic (CT) scan performed at an outside hospital demonstrated a large (4.5 cm) tumor in the pancreatic head extending into the uncinate process and involving the superior mesenteric vein (SMV) at the level of the first jejunal branch with bulky peripancreatic lymphoadenopathy (Figure 1A). The initial fine needle aspiration (FNA) biopsy of the mass in head of the pancreas performed at the outside institution was considered non-diagnostic. He also underwent endoscopic retrograde cholangiopancreatography (ERCP) and endobiliary decompression at local hospital which showed an ampullary mass with distal biliary stricture. The ampullary biopsy showed superficial fragments of atypical glandular epithelium suspicious for adenocarcinoma. He subsequently underwent a staging laparoscopy at outside hospital and was found to have no evidence of extrapancreatic metastatic disease. Since his primary pancreatic tumor involves the superior mesenteric vein, he was deemed to have locally advanced disease and was referred to our institution for second opinion and treatment. Due to the radiographic appearances of a large primary tumor and prominent peripancreatic lymphoadenopathy combined with his young age are somewhat unusual for pancreatic ductal adenocarcinoma, the possibility of a pancreatic neuroendocrine carcinoma was clinically considered. Endoscopic ultrasound guided FNA of the pancreatic head mass was performed and showed a poorly differentiated carcinoma with neuroendocrine differentiation (positive for synaptophysin and chromogranin). He also underwent a repeat endoscopy of the upper gastrointestinal tract in our hospital. A

polypoid mass was identified at the ampulla of Vater (Figure 1B). The repeat endoscopic biopsy from the ampullary mass showed a moderately differentiated adenocarcinoma which was negative for both chromogranin and synaptophysin. His CA19.9 is 44 U/ml (normal 0-37U/ml) with a modest elevation in serum chromogranin-A (288 ng/ml). All other serum tumor markers, including carcinoembryonic antigen (CEA), insulin, glucogon, gastrin, and pancreatic peptide, were within the normal range. He underwent pylorus preserving pancreaticoduodenectomy with retroperitoneal lymphadenectomy, segmental resection of SMV with left internal jugular vein interposition graft and cholecystectomy.

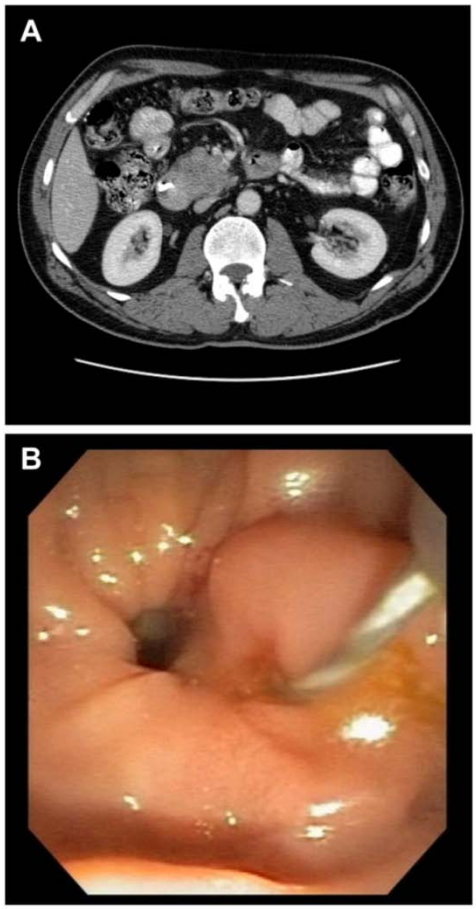

Figure 1 A.Computed tomographic (CT) scan showed a large mass in the pancreatic head extending into the uncinate process and involving the superior mesenteric vein (SMV) with peripancreatic lymphoadenopathy. B. Endoscopic picture of the mass at the ampulla of Vater.

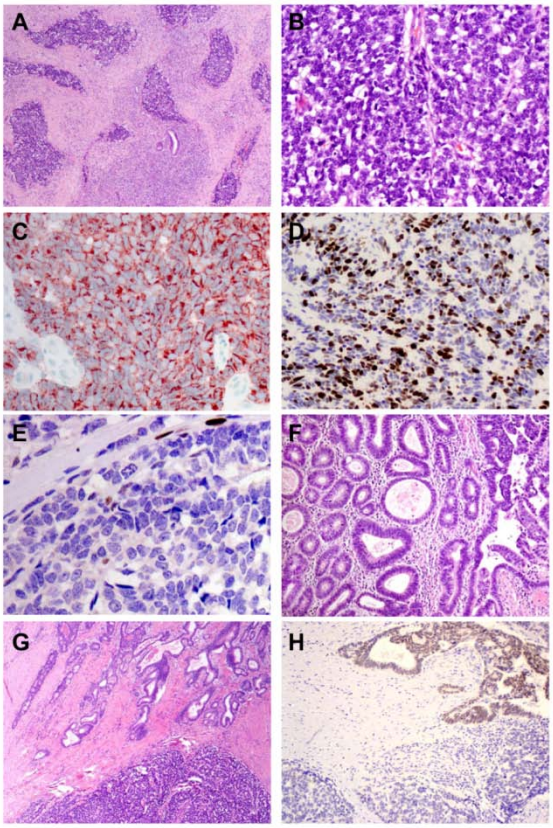

Figure 2 Representative micrographs show small cell neuroendocrine carcinoma (NEC) of the pancreas with infiltrative nodule growth pattern invading the pancreas (A), small-sized to medium-sized cells with minimal cytoplasm, inconspicuous nucleoli and many mitoses (B). The small cell NEC is positive for chromogranin A (C) and has Ki-67 labeling index of 60% (D), but is negative for retinoblastoma (Rb) protein (E). The positive nuclear staining for Rb protein in stromal cells serves as internal positive control. Representative micrographs shows a moderately differentiated adenocarcinoma (intestinal type) of the ampulla of Vater arising in a tubular adenoma (F) and the interphase between the adenocarcinoma and pancreatic small cell NEC in the wall of the duodenum (G). The ampullary adenocarcinoma is positive for CDX-2 and pancreatic small cell NEC is negative for CDX-2. (Original magnifications: 40× for A and G; 200× for B, C and E; 100× for D, F, and H).

Gross examination of the pancreaticoduodenectomy revealed a tan, firm, ill-defined mass (4.5 x 3.5 x 3.2 cm) in the head of the pancreas. The pancreatic mass

grossly involved the peripancreatic adipose tissue and focally involved the duodenal wall, invaded into the lumen of the resected segment of SMV and obstructed the pancreatic duct, but did not involve the common bile duct. In addition, a 2.1 x 2.1 cm mass was also identified in the ampulla of Vater. The ampullary mass grossly invaded into the duodenal wall and focally merges with the mass in the head of the pancreas. Microscopically, the pancreatic mass showed a small cell carcinoma with a diffuse, infiltrative nodular growth pattern, multiple areas of necrosis and brisk mitotic activity (39 mitoses/10 high power fields, Figure 2A, 2B). Tumor invaded into the retroperitoneal fibroadipose tissue, the muscularis propria of duodenum and the lumen of the resected segment of SMV (tumor thrombus), which extended to the SMV resection margin microscopically. Extensive lymphovascular and perineural invasion are present. The tumor cells were small to medium in size with hyperchromatic nuclei, finely granular chromatin pattern, inconspicuous nucleoli and scant cytoplasm (Figure 2B). The tumor cells were diffusely positive for chromogranin (Figure 2C), synaptophysin (data not shown) with a Ki-67 labeling index of 60% (Figure 2D). Therefore the diagnosis of pancreatic small cell NEC was rendered. The pancreatic small cell NEC was also positive for Bcl-2 and was negative for p53 (data not shown), retinoblastoma (Rb) protein (Figure 2E) and CDX2 (Figure 2H). No adenocarcinoma component is identified in the pancreatic mass. Sections from the ampullary tumor showed a conventional moderately differentiated adenocarcinoma (intestinal type) arising in a tubular adenoma, which is morphologically different from the pancreatic small cell NEC (Figure 2F). Both ampullary adenocarcinoma and the pancreatic small cell NEC invade into the muscularis propria of the duodenum, where the two tumors collided. However the pancreatic small cell NEC does not involve the submucosa or ampullary mucosa and did not intermix with the ampullary adenocarcinoma (Figure 2G). The ampullary carcinoma is negative for chromogranin, synaptophysin, p53, and Rb protein, but positive for Bcl-2 and CDX-2 (Figure 2H). Metastatic small cell NEC was present in 6 of 40 regional lymph nodes and all lymph nodes were negative for metastatic adenocarcinoma. Therefore the diagnosis of small cell NEC of the pancreas with synchronous adenocarcinoma of ampulla of Vater was rendered in final pathology diagnosis.

Patient recovered uneventfully after the surgery and was discharged home on postoperative day #8. Postoperatively, he received adjuvant radiation therapy (50.4 Gy, 1.8 Gy/fraction delivered five days per week, Monday-Friday, over a period of five and half weeks) and total of five cycles of chemotherapy consisting of cisplatin (30 mg/m^2) and irinotecan (65mg/m^2) on days #1 and #8 of a 21-day cycle. The patient is doing well with no evidence of recurrence or metastasis during the follow up of 117 months after the surgery.

Discussion

Small cell NEC of the pancreas is extremely rare. Only few reports have been published with fewer than 50 cases reported in the English literature [6-13]. This is the first reported case of pancreatic small cell NEC with synchronous adenocarcinoma of the ampulla of Vater, who was successfully treated with pancreaticoduodenectomy and adjuvant chemoradiation therapy with a long survival. According to the previous studies, small cell NECs are usually non-functional and are most often located in the head of the pancreas with an average age of 60 years. Similar to our patient, patients with small cell NECs commonly present with abdominal pain,

jaundice and weight loss[3, 8, 10].

Although the adenocarcinoma of ampulla of Vater collided focally with the small cell NEC of the pancreas in the muscularis propria of duodenum in our case, the two tumors had distinct morphology and did not intermix with each other. The histology of his ampullary mass was a moderately differentiated adenocarcinoma that was confined in the duodenal wall without invasion into the pancreatic parenchyma or peripancreatic soft tissue. Adenomatous epithelium was present at the junction between the ampullary mass and the duodenal mucosa, but there is no NEC component identified in the entirely submitted ampullary mass. On the other hand, the pancreatic mass showed a pure small cell NEC with no adenocarcinoma component identified in 18 sections submitted from the pancreatic mass and adjacent pancreatic/peripancreatic soft tissue. By immunohistochemistry, the pancreatic small cell NEC was diffusely positive for chromogranin and synaptophysin and was negative for CDX-2. In contrast, the adenocarcinoma at the ampulla of Vater is diffusely positive for CDX-2 and was negative for both chromogranin and synaptophysin. Thus it is less likely that pancreatic small cell NEC is arising from the adenocarcinoma of the ampulla of Vater.

The origin of high-grade NECs of the pancreas is uncertain. Although it is possible that well-differentiated pancreatic NET may rarely transform into a high-grade pancreatic NECs and pancreatic ductal carcinoma (PDAC) may also give arise to high grade pancreatic NEC, recent genetic and immunohistochemical study by Yachida et al suggest that high-grade pancreatic NECs are distinct from well-differentiated pancreatic NETs as well as pancreatic ductal adenocarcinoma (PDAC), but have a similar profile in the genetic alterations to the small cell carcinoma of lung [10]. Many genetic alterations that are characteristic for PDAC, such as activating Kras mutations and loss of CDKN2A/p16 and SMAD4/DPC4, are infrequently found in high-grade pancreatic NECs [3, 10, 14]. In contrast to well-differentiated pancreatic NETs which have no mutations in p53 or Rb genes, mutations in p53 and Rb genes are identified in 100% and 89% respectively in the small cell NECs of the pancreas; 90% and 60% respectively in large cell NECs of the pancreas. High-grade pancreatic NECs also have higher frequency of Bcl-2 overexpression than PDACs or well differentiated NETs in their study [10]. Consistent with their study, the pancreatic small cell NEC in our case was positive for Bcl-2 and lost expression of Rb protein. However our case is negative for p53 by immunohistochemistry.

Pancreatic small cell NEC is a highly aggressive neoplasm with a dismal prognosis and patient usually died within 1 year after diagnosis[3, 8, 10], except three cases reports of 36, and 56 and 173 months of survival after surgery [11-13]. Recent study conducted by Winter et al showed that patients with pancreatic small cell NEC may benefit from post-operative cisplatin and etoposide-based chemoradiation therapy [13]. Our patient was successfully treated with pancreaticoduodenectomy and adjuvant cisplatin-based chemoradiation and was alive with no evidence of disease at 117 months. Given the limited number of cases in these studies, further studies are needed to identify effective treatment for small cell NEC of the pancreas.

Conclusions

We reported an unusual case of small cell neuroendocrine carcinoma of the pancreas with a synchronous moderately differentiated adenocarcinoma of the ampulla of Vater, who was successfully treated with surgery and adjuvant cisplatin-based chemoradiation

therapy and was disease-free at 117 months after the surgery.

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